REMARKS

Priority

The priority data has been added in the specification with specific reference to prior applications, including the relationship of the present application to the prior applications. Entry of this amendment is respectfully requested.

Drawings

The drawings were objected to on the grounds that Figures 1A to 1H, 2A-1 to 2A-9, and 2B-1 to 2B-9 are depicted, but the "Brief Description of the Drawings" refers to Figures 1 and 2. In light of the amendments to the specification, Applicants respectfully request withdrawal of this objection.

Claim Rejections Under 35 U.S.C. § 102

Claims 21-23 and 27-29 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,965,350 to Inoue *et al.* ("Inoue"). In particular, the Examiner asserts that Inoue's disclosure of 3-(5'O-triphosphoryl-beta-D-deoxyribo-furanosyl) 2,7-dioxopyrido[2,3-d]pyrimidine which may be modified at the 2' position to include a hydroxyl moiety anticipates a nucleotide triphosphate comprising a covalently attached electron transfer moiety. In particular, the Examiner has asserted that hydroxyl groups (-OH) can be considered ETMs. The Applicants respectfully disagree and offer several scientific articles that show that hydroxyl groups should not be considered as ETMs.

Applicants recognize that any molecule can be oxidized or reduced if subjected to sufficiently large positive or negative voltages. Certainly, neither the examiner nor the applicants would assert that any molecule or pendant group should be considered an

ETM. Applicants contend that a molecule or pendant group can be considered to be an ETM if that molecule or pendant group can be induced to donate or accept an electron under the conditions disclosed in the present application. In the case of the present invention, such conditions comprise voltages in the range commonly used in electron transfer or electrochemistry experiments, *e.g.*, from approximately -1 volt to +1 volt. Voltages beyond these extremes are not commonly explored because aqueous solvents break down outside this voltage range.

Applicants request that the examiner consider the experimental results in the following two papers exploring the electrochemical oxidation potentials of alcohols. Hampson, *et al.*, 1981, J. Chem. Soc., Faraday Trans., 1: 987-995 ("Hampson"; enclosed herewith as Exhibit 1) explore the oxidation of methanol (CH_3OH) at larger voltages than can be used in aqueous environments by using trifluoromethanesulfonic acid monohydrate (TFMSAMH), which is extremely inert, as the solvent. Figure 3 of Hampson illustrates a cyclic voltammogram for 0.6M methanol at a platinum electrode. No distinct peaks can be seen in the voltammogram as would be expected at this high concentration of methanol (typical electrochemical experiments are usually millimolar or less) if hydroxyl groups were ETMs. Hampson attributes the large rise in current at voltages greater than 1 volt to the likely oxidation of methanol:

> At potentials more anodic than 1.0 V much higher anodic currents are recorded than in methanol-free solutions. No discreet peak is observed and the current increases rapidly beyond 1.4 V due to the oxygen evolution reaction.

Hampson finds that methanol oxidation can be readily observed only when water is added to the solvent. For example, Figure 5 shows the cyclic voltammogram when

10.5% water is added. In this case, an oxidation peak is observed at approximately 1 volt. Hampson attributes this to the oxidation of methanol.

In the second paper, Gao et al., 1989, J. Electroanal. Chem., 272, 161-178, ("Gao"; enclosed herewith as Exhibit 2), perform similar experiments on platinum electrodes in anhydrous methanol or ethanol, again at rather large voltage extremes (-0.1 to +1.5 V). Gao et al., study the methanol oxidation using an optical technique, Fourier transform infrared (FTIR) spectroscopy. The FTIR technique allows Gao to observe the generation of oxidation products when the alcohols are oxidized. Figure 1 depicts the products observed for methanol. Referring to Figure 1, a sharp downward doublet peak is observed at 1716 and 1730 cm-1. Gao attributes this to doublet peak to carbonyl formation (C=O). Because these peaks are only observed at applied voltages greater than 1 V, methanol is only oxidized at rather extreme voltages, e.g., greater than 1 V. The results for ethanol oxidation are shown in Figure 5. In this case, the oxidation products give rise to a downward peak at 954 cm-1, which again, is observed only for applied voltages of 1 volt and greater.

These two papers demonstrate that hydroxyl groups, such as those present in methanol and ethanol are not readily oxidized, and thus cannot be considered ETM's as defined by the applicants in the present application.

The applicants wish to bring two other papers to the attention of the Examiner. These two papers represent more traditional electrochemical studies at voltages less than one volt and explore the oxidation or reduction of molecules using methanol as a solvent. As the examiner surely appreciates, the solvent employed in electrochemical experiments

must not, itself, interfere with the reaction under study; that is, it cannot be electroactive in the voltage range of the experiment.

The applicants are not using subsequent work to supplement the disclosure of the application; rather, the subsequent work is presented to demonstrate that hydroxyl groups, such as those present in methanol and ethanol are not readily oxidized, and thus, cannot be considered ETM's as defined by the applicants in the present application. *See* In re Wilson, 135 USPQ 442, 444 (CCPA 1962); Ex parte Obukowicz, 27 USPQ 2d 1063 (BPAI 1993); and Gould v. Quigg, 3 USPQ 2d 1302,1305 (Fed. Cir. 1987):

> it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the later dated publication was not offered as evidence for this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative.

Ramirez-Garcia, et al., 2004, Anal. Chem., 76:503-512 ("Ramirez-Garcia") explores the use of new composite electrode materials. The bottom half of Figure 4 shows cyclic voltammetry results for two different composite electrode material using methanol as the solvent. The oxidation and reduction peaks are those associated with the electrochemistry of ferrocene (a molecule that fits Applicants' definition of ETM). Clearly, the methanol solvent does not interfere with this study of ferrocene; despite its extremely high concentration (essentially 100%), it is not oxidized nor reduced.

Dang et al., 1997, J. Electroanalytical Chemistry, 437: 53-59 ("Dang"; enclosed herewith as Exhibit 4) study the electrochemistry of a therapeutic molecule 10-methylphenothiazine (MPT) which exhibits solubility problems in neutral pH aqueous solvents. Dang achieves acceptable solubility using methanol/water mixtures and by

trapping the MPT molecules in beta-cyclodextrin. Figure 3 shows the results of cyclic voltammetry experiments where the methanol was varied from 10% (v/v) to 40% in water. Clearly, no electrochemical reactions of the methanol interfere with the intended system of study: the redox properties of MPT (another example of a molecule that fits Applicants' definition of ETM) at applied voltages up to 1.0 volt.

Finally, while the above two examples have dealt with oxidation studies at positive voltages, Fussing et al., 1998, Acta Chemica Scandinavica, 52: 328-337 ("Fussing"; enclosed herewith as Exhibit 5) study reduction reactions of eight different cinnamic acid esters. Methanol as an inert solvent for reductive electrochemistry is clearly demonstrated in this study. For example, Figure 2 shows the results of cyclic voltammetry for two different cinnamates in methanol at a mercury electrode over the voltage range of -1.2 V to -2.0 V. There is clearly no interference in the measurement of cinnamate reduction at reductive voltages as large at –2.0 volts.

For an anticipation rejection under 35 U.S.C. §102(b) to be proper, a single reference must expressly or inherently disclose each and every element of a claim. In re Paulsen, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing Richardson v. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

As pointed out above, the Examiner has not pointed to any disclosure in Inoue that teaches the attachment of an electron transfer moiety to a nucleotide triphosphate. Moreover, Applicants assert that it is clear from the results described in Exhibits 1-5 that hydroxyl groups cannot be considered as ETMs in the sense intended by the applicants.

Accordingly, the Examiner has not carried his burden under §102(b), and therefore Applicants respectfully request withdrawal of the rejection.

Claims 21, 22, 24, 25, 27, 28, 30 and 31 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,278,043 to Bannwarth *et al.* ("Bannwarth").

As amended Claims 21, 22, 24, 25, 27, 28, 30 and 31 disclose nucleotide triphosphates comprising a covalently attached electron transfer moiety.

Bannwarth et al., do not teach or disclose nucleotide triphosphates comprising a covalently attached electron transfer moiety. Accordingly, Bannwarth et al., do not anticipate the claims as amended. Applicants respectfully request withdrawal of the rejection.

Please direct further questions in connection with this petition to the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

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By: Renee M. Kosslak

Renee M. Kosslak, Reg. No. 47,717 for
Robin M. Silva, Reg. No. 38,304

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Customer No.: 32940
Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989
Facsimile: (415) 398-3249